Kam 09/982,544

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=> d his 1

     (FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     14:49:17 ON 30 JUN 2003)
L46           41 DUP REM L34 (68 DUPLICATES REMOVED)

=> d que l35
L1             1 SEA FILE=REGISTRY THIAZOLIDINEDIONE/CN
L2          5909 SEA THIAZOLIDINEDIONE
L3           291 SEA SCHULMAN I?/AU
L4           615 SEA BISCHOFF E?/AU
L5           144 SEA TANGIRALA R?/AU
L7             2 SEA (L4 OR L5 OR L6) AND L3
L8          1155 SEA LXR
L9            17 SEA (L4 OR L5 OR L6) AND L8
L10            6 SEA L9 AND DIABET?
L14          987 SEA LIVER# (5A) X(5A) RECEPTOR#
L25           65 SEA L7 OR (L10 OR L11 OR L12 OR L13) OR (L15 OR L16 OR L17) OR
                 L25
L30            9 SEA (L6 OR L14) AND L3
L31           65 SEA DIABET? AND (L6 OR L14)
L32           51 SEA L31 NOT ATHEROSCLER?
L33           15 SEA L32 NOT PY>2001
L34           76 SEA L28 OR L30 OR L33
L35           41 DUP REM L34 (35 DUPLICATES REMOVED)


=> d ibib abs l35 1-41

L35 ANSWER 1 OF 41 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2003:417731 HCAPLUS
DOCUMENT NUMBER:          139:06[illegible]
TITLE:                    Preparation of 5-(benzylidene)rhodanines and analogs
                          as antidiabetics and antitumor agents
INVENTOR(S):              Fahl, Magnus; Tachdjian, Catherine; Spruce, Lyle W.;
                          Al-Shamma, Hussien A.; Boudjelal, Mohamed; Fanjul,
                          Andrea N.; Wiemann, Torsten R.; Pleynet, David P. M.
PATENT ASSIGNEE(S):       Maxia Pharmaceuticals, Inc., USA
SOURCE:                   PCT Int. Appl., 118 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ----------------  ----  --------      ---------------  --------
     WO 2003043948     A1    20030530      WO 2002-US36583  20021115
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
            GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
            PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
            UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
            CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
            PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
            NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 2001-334794P  P  20011116

                    Search completed by David Schreiber  308-4292
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Kam 09/982,944

US 2002-362702P P 20020308
US 2002-362732P P 20020308

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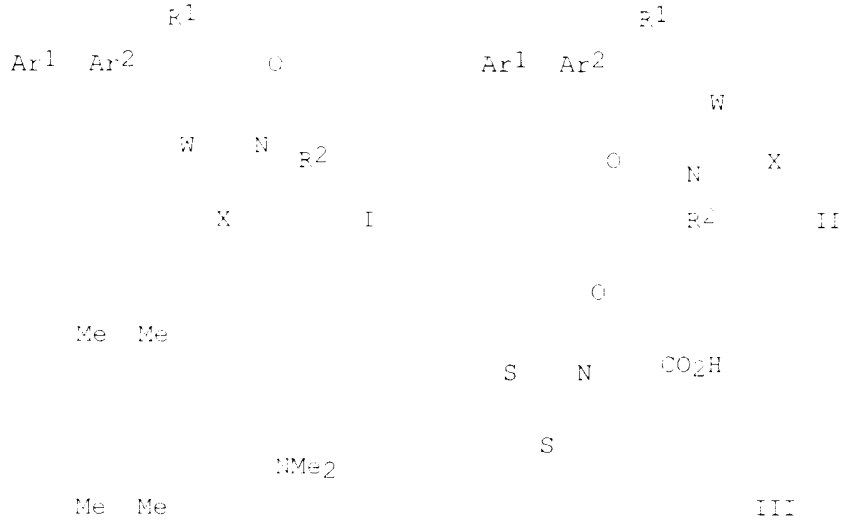


AB Title benzylidene-substituted 2-thioxo-4-oxothiazolidines and analogs I and II [wherein Ar1 = 2-(R7)-4-(R5)-5-(R6)C6H2 optionally substituted with R8; Ar2 = (hetero)aryl; W = S, O, or NR3; X = O or S; R1 = H or (un)substituted org. radical comprising 1-4 C's; R2 = (un)substituted org. radical comprising 1-12 C's; R3 = H or (un)substituted org. radical comprising 1-12 C's; C2R5R6 = 5-7 membered non-arom. ring optionally comprising 1-2 heteroatoms; R7 and R8 = independently H or (un)substituted alkyl or amino; and pharmaceutically acceptable salts thereof] were prepd. as **liver X receptor** (**LXR**), peroxisome proliferator-activated **receptor** .gamma. (PPAR.gamma.), protein kinase Akt/PKB (AKT-1/PKBa) inhibitors. For example, esterification of 6-hydroxynaphthoic acid with EtOH (98 %), followed by protection with triflic anhydride in CH2Cl2 gave 6-(trifluoromethanesulfonyloxy)naphthalene-2-carboxylic acid Et ester (100 %). Redn. of the ester to the alc. (72 %) using DIBAL, conversion to the aldehyde (94 %) with PCC, and Suzuki coupling with (3-dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-yl)boronic acid provided the 6-(tetrahydronaphthalenyl)naphthalene-2-carboxaldehyde (71 %). Coupling of the aldehyde with rhodanine-3-acetic acid in the presence of piperidine and acetic acid in toluene afforded III (33 % yield, 99.5 % purity). The latter antagonized both **LXR** and PPAR.gamma. activation in vitro in a dose-dependent fashion, reaching inhibition values of about 85-90 % at 10 .mu.M. Oral administration of III to rats maintained on a high cholesterol atherogenic diet resulted in significant redns. in total serum cholesterol and low d. lipoprotein cholesterol levels with accompanying elevations in high d. lipoprotein cholesterol levels compared to controls. In addn., III displayed selective potency against various human cancer cell lines; e.g., at a concn. of 10 .mu.M, about 90 % of breast cancer cells were killed compared to about 50 % of other cell lines studied. Thus, I and II are useful in the treatment of

diseases, such as, cancer, metabolic disorders, Type 2 Diabetes, dyslipidemia, and/or hypercholesterolemia.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 2 OF 41 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:310597 HCAPLUS
DOCUMENT NUMBER: 138:314592
TITLE: Methods for affecting various diseases utilizing **LXR** compounds
INVENTOR(S): **Schulman, Ira G.; Bischoff, Eric D. ; Tangirala, Rajendra K.**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 33 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003073614	A1	20030417	US 2001-982544	20011017

PRIORITY APPLN. INFO.: US 2001-982544 20011017

AB The invention relates to methods for elevating high d. lipoprotein (HDL) plasma levels, decreasing the absorption of dietary cholesterol in the intestine, decreasing the plasma level of low d. lipoprotein (LDL), and increasing the conversion of cholesterol to bile acids, utilizing **LXR**.beta. selective agonists, usually without elevating the plasma levels of triglycerides. Also provided are methods of using such agonists to treat metabolic diseases alone or in combination with other active agents. Also provided are methods for **decreasing hyperglycemia** and **insulin resistance** methods for **treating type II diabetes**, and methods for **treating type II diabetes** and **reducing** the **cardiovascular complications** of **type II diabetes**, utilizing an **LXR** agonist. Further provided are methods for treating obesity and methods for **treating** the complications of obesity including **type II diabetes**, cardiovascular disease, hyperlipidemia, and hypertension, **administering** an **LXR**.alpha.-selective antagonist.

L35 ANSWER 3 OF 41 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:276503 HCAPLUS
DOCUMENT NUMBER: 138:362624
TITLE: Assays for **liver X receptor** (**LXR**) modulators
INVENTOR(S): Gustafsson, Jan- Ke; Schuster, Gertrud; Nebb, Hilde Irene
PATENT ASSIGNEE(S): Karo Bio AB, Swed.
SOURCE: Brit. UK Pat. Appl., 36 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

GB 2341-66	A1	20030314	GB 2001-27132	20011112
PRIORITY APPLN. INFO.:			GB 2001-27132	20011112

AB Assays for identifying agents for the **treatment** of **diabetes** or disorders of fatty acid or cholesterol metab., by identifying modulators (ligands, agonists or antagonists) that bind to or modulate the biol. activity of **liver X receptor** alpha or beta (**LXR**.alpha. or **LXR**.beta.). Such modulators may alter the amt. of at least one of SREBP-1, cholesterol 7.alpha.-hydroxylase (Cyp7A), fatty acid synthetase, human cholesterol ester transfer protein (CETP), **LXR**.alpha. or **LXR**.beta. protein or mRNA levels. The assay may be performed in hepatocyte, adipocyte or preadipocyte cells. The assay may be performed in combination with a retinoid X receptor (RXR). Use of agents identified by such assays in the prepn. of medicaments and methods of **treating diabetes** are also claimed.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 4 OF 41 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 2003007393 MEDLINE
DOCUMENT NUMBER: 22401814 PubMed ID: 12414791
TITLE: Antidiabetic action of a **liver x receptor** agonist mediated by inhibition of hepatic gluconeogenesis.
AUTHOR: Cao Guoqing; Liang Yu; Broderick Carol L; Oldham Brian A; Beyer Thomas P; Schmidt Robert J; Zhang Youyan; Stayrook Keith R; Suen Chen; Otto Keith A; Miller Anne R; Dai Jiannong; Foxworthy Patricia; Gao Hong; Ryan Timothy P; Jiang Xian-Cheng; Burris Thomas P; Eacho Patrick I; Etgen Garret J
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly & Company, Indianapolis, Indiana 46285, USA.. guoqing_cao@lilly.com
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2003 Jan 10) 278 (2) 1131-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030107
Last Updated on STN: 20030308
Entered Medline: 20030307

AB The oxysterol **receptors LXR** (**liver X receptor**)-alpha and LXRbeta are nuclear receptors that play a key role in regulation of cholesterol and fatty acid metabolism. We found that LXRs also play a significant role in glucose metabolism. **Treatment** of **diabetic** rodents with the **LXR** agonist, T0-1317, resulted in dramatic **reduction** of **plasma glucose**. In insulin-resistant Zucker (fa/fa) rats, T0-1317 significantly improved insulin sensitivity. Activation of **LXR** did not induce robust adipogenesis but rather inhibited the expression of several genes involved in hepatic gluconeogenesis, including phosphoenolpyruvate carboxykinase (PEPCK). Hepatic glucose output was dramatically reduced as a result of this regulation. Nuclear run-on studies indicated that transcriptional repression was primarily responsible for the inhibition of PEPCK by the **LXR** agonist. In addition, we show that the regulation of the liver gluconeogenic pathway

by **LXR** agonists was a direct effect on hepatocytes. These data not only suggest that LXRs are novel targets for diabetes but also reveal an unanticipated role for these receptors, further linking lipid and glucose metabolism.

L35 ANSWER 5 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003185720 EMBASE
TITLE: Rationale and options for combination **therapy** in the **treatment** of **Type 2 diabetes**.
AUTHOR: Van Gaal L.F.; De Leeuw I.H.
CORPORATE SOURCE: L.F. Van Gaal, University Hospital of Antwerp, Faculty of Medicine, Dept. Diabetology, Metab./Clin. N., Wilrijkstraat 10, 2650 Edegem (Antwerp), Belgium. luc.van.gaal@uza.be
SOURCE: Diabetologia, (1 Mar 2003) 46/SUPPL. 1 (M44-M50).
Refs: 43
ISSN: 0012-186X CODEN: DBTGAJ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Endocrinology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Pharmacological **therapy** for **Type 2** (non-insulin-dependent) **diabetes** mellitus aims at controlling hyperglycaemia to delay or prevent complications associated with the disease. Most patients with Type 2 diabetes present with both stimulated insulin deficiency and insulin resistance. In general, the former can manifest as postprandial hyperglycaemia and the latter as fasting hyperglycaemia, though a definitive association has not been established. Emerging data show a high failure rate of long-term monotherapy and establishes the significance of mealtime glycaemia and the role of postprandial glucose excursions in the development and progression of **vascular complications**. To overcome such failures of monotherapy and to address the different underlying defects of the pathology of **Type 2 diabetes**, a combined **therapy** of oral antidiabetic agents with complementary modes of action should be considered. Currently used oral antidiabetic agents such as sulphonylureas, biguanides (metformin) and the thiazolidinediones (rosiglitazone, pioglitazone) commonly target fasting hyperglycaemia and have limited additive effects on postprandial glycaemia. In contrast, .alpha.-glucosidase inhibitors can reduce postprandial hyperglycaemia but gastrointestinal side effects restrict their use. The development of new agents to control postprandial glucose excursions could be considered as an additional objective for the management of Type 2 diabetes. To this end new short-acting enhancers of insulin secretion such as repaglinide (benzoic acid derivative) and nateglinide (amino acid derivative) have been developed. The combination of such agents with other complementary modes of action, e.g. an insulin sensitizer, could target better major underlying defects of Type 2 diabetes and thereby provide a better approach for controlling the entire glycaemic risk.

L35 ANSWER 6 OF 11 MEDLINE
ACCESSION NUMBER: 12738041 MEDLINE
DOCUMENT NUMBER: 22668944 PubMed ID: 12738511
TITLE: Lessons learned from landmark trials of type 2 diabetes mellitus and potential applications to clinical practice.
AUTHOR: Drexler Andrew J

CORPORATE SOURCE: Mount Sinai Diabetes Center, Mount Sinai Medical Center, 1200 5th Ave, Box 1616, New York, NY 10029, USA.. andrew_drexler@smtplink.mssm.edu
SOURCE: POSTGRADUATE MEDICINE, (2003 May) Spec No 15-26. Ref: 56 Journal code: 0401147. ISSN: 0032-5481.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW) (REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030606 Last Updated on STN: 20030620 Entered Medline: 20030619

AB Landmark studies have demonstrated that diabetes is a significant risk factor for cardiovascular disease and mortality. Strong relationships exist between insulin resistance/hyperglycemia and mortality, microvascular **complications**, and **cardiovascular complications**. Lipid abnormalities frequently associated with type 2 diabetes and insulin resistance include low high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride levels. Lowering low-density lipoprotein cholesterol levels has been shown to improve the prognosis of patients with diabetes, and increasing HDL-C levels will significantly reduce the incidence of major coronary events. Higher levels of insulin sensitivity are associated with thinner intimal-medial thickness of the carotid artery, which indicates less atherosclerosis. Thiazolidinediones increase insulin sensitivity, decrease intimal-medial thickness, and appear to have inhibitory effects on the progression of atherosclerotic lesions. It is hoped that by preventing the onset of diabetes in high-risk individuals--and improving insulin sensitivity with lifestyle changes or pharmacologic **treatment**--the profound complications of **type 2 diabetes** will be **prevented** or delayed, as well.

L35 ANSWER 7 OF 41 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002441778 MEDLINE
DOCUMENT NUMBER: 22287434 PubMed ID: 12193639
TITLE: Regulation of cholesterol homeostasis and lipid metabolism in skeletal muscle by **liver X receptors**.
AUTHOR: Muscat George E O; Wagner Brandee L; Hou Jinchao; **Tangirala Rajendra K; Bischoff Eric D**; Rohde Paul; Petrowski Mary; Li Jiali; Shao Gang; Mahendray Griffin; **Schulman Ira G**
CORPORATE SOURCE: N-Gene Therapeutics, Inc., 4757 Nexus Centre Drive, San Diego, CA 92121, USA.. g.muscat@imb.uq.edu.au
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Oct 25) 277 43[illegible] 40722-8. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021026 Last Updated on STN: [illegible] Entered Medline: [illegible]

AB Recently, studies have identified the **liver X**

Search completed by David Schreiber [illegible]

receptors (LXRalpha and LXRbeta) as important regulators of cholesterol and lipid metabolism. Although originally identified as liver-enriched transcription factors, LXRs are also expressed in skeletal muscle, a tissue that accounts for approximately 40% of human total body weight and is the major site of glucose utilization and fatty acid oxidation. Nevertheless, no studies have yet addressed the functional role of LXRs in muscle. In this work we utilize a combination of in vivo and in vitro analysis to demonstrate that LXRs can functionally regulate genes involved in cholesterol metabolism in skeletal muscle. Furthermore we show that treatment of muscle cells in vitro with synthetic agonists of LXR increases the efflux of intracellular cholesterol to extracellular acceptors such as high density lipoprotein, thus identifying this tissue as a potential important regulator of reverse cholesterol transport and high density lipoprotein levels. Additionally we demonstrate that LXRalpha and a subset of LXR target genes are induced during myogenesis, supporting a role for LXR-dependent signaling in the differentiation process.

L25 ANSWER 5 OF 41 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002464942 MEDLINE
DOCUMENT NUMBER: 22199837 PubMed ID: 12193651
TITLE: Identification of macrophage **liver X receptors** as inhibitors of atherosclerosis.
AUTHOR: **Tangirala Rajendra K; Bischoff Eric D;** Joseph Sean B; Wagner Brandee L; Walczak Robert; Laffitte Bryan A; Daige Chris L; Thomas Diane; Heyman Richard A; Mangelsdorf David J; Wang Xuping; Lusis Aldons J; Tontonoz Peter; **Schulman Ira G**
CORPORATE SOURCE: X-Ceptor Therapeutics, 4757 Nexus Center Drive, San Diego, CA 92121, USA.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2002 Sep 3) 99 (18) 11896-901. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020913
Last Updated on STN: 20030105
Entered Medline: 20020927

AB Recent studies have identified the **liver X receptors** (LXR alpha and LXR beta) as important regulators of cholesterol metabolism and transport. LXRs control transcription of genes critical for a range of biological functions including regulation of high density lipoprotein cholesterol metabolism, hepatic cholesterol catabolism, and intestinal sterol absorption. Although LXR activity has been proposed to be critical for physiologic lipid metabolism and transport, direct evidence linking LXR signaling pathways to the pathogenesis of cardiovascular disease has yet to be established. In this study bone marrow transplantations were used to selectively eliminate macrophage LXR expression in the context of murine models of atherosclerosis. Our results demonstrate that LXRs are endogenous inhibitors of atherogenesis. Additionally, elimination of LXR activity in bone marrow-derived cells mimics many aspects of Tangier disease, a human high density lipoprotein deficiency, including aberrant regulation of cholesterol transporter expression, lipid accumulation in macrophages, splenomegaly, and increased atherosclerosis. These results identify LXRs as targets for intervention in cardiovascular disease.

L35 ANSWER 4 OF 41 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2002692396 MEDLINE
DOCUMENT NUMBER: 22341172 PubMed ID: 12453904
TITLE: Mechanisms of the triglyceride- and cholesterol-lowering effect of fenofibrate in hyperlipidemic type 2 diabetic patients.
AUTHOR: Fercheron Fabien; Cachefo Ana; Thevenon Sylvie; Pinteur Claudie; Beylot Michel
CORPORATE SOURCE: INSERM U 499, Faculte RTH Laennec, Rue G Paradin, 69008 Lyon, France.
SOURCE: DIABETES, (2002 Dec) 51 (12) 3486-91.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021214
Last Updated on STN: 20021227
Entered Medline: 20021220

AB In humans, the precise mechanisms of the hypolipidemic action of fenofibrate, a peroxisome proliferator-activated receptor-alpha agonist, remain unclear. To gain insight on these mechanisms, we measured plasma lipids levels, lipids synthesis (hepatic de novo lipogenesis and cholesterol synthesis), and mRNA concentrations in circulating mononuclear cells (RT-PCR) of hydroxymethylglutaryl (HMG)-CoA reductase, LDL receptor, LDL receptor- related protein (LRP), scavenger receptor class B type I (SR-BI), ABCAI, and **liver X receptor** (**LXR**)-alpha in 10 control subjects and 9 hyperlipidemic type 2 diabetic patients. Type 2 diabetic subjects were studied before and after 4 months of fenofibrate administration. Fenofibrate decreased plasma triglycerides (P < 0.01) and total cholesterol (P < 0.05) concentrations and slightly increased HDL cholesterol (P < 0.05). Hepatic lipogenesis, largely enhanced in diabetic subjects (16.1 +/- 2.1 vs. 7.5 +/- 1.6% in control subjects, P < 0.01), was decreased by fenofibrate (9.8 +/- 1.5%, P < 0.01). Fractional cholesterol synthesis was normal in diabetic subjects (3.5 +/- 0.4 vs. 3.1 +/- 0.5% in control subjects) and was unchanged by fenofibrate (3.3 +/- 0.3%). Absolute cholesterol synthesis was, however, increased in diabetic subjects before and after fenofibrate (P < 0.05 vs. control subjects). HMG-CoA reductase, LDL receptor, LRP, and SR-BI mRNA concentrations were not different in type 2 diabetic and control subjects and were unchanged by fenofibrate. **LXR**-alpha mRNA levels were increased (P < 0.05) by fenofibrate. ABCAI mRNA concentrations, which were **decreased** in **diabetic** subjects (P < 0.05) before fenofibrate, were increased (P < 0.05) by fenofibrate to values comparable to those of control subjects. The plasma triglyceride-lowering effect of fenofibrate is explained in part by a decrease in hepatic lipogenesis, the moderate fall in total plasma cholesterol is not explained by a reduction of whole-body cholesterol synthesis, and the increase in **LXR**-alpha and ABCAI mRNA levels suggests that fenofibrate stimulated reverse cholesterol transport.

L35 ANSWER 5 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
ACCESSION NUMBER: 2[illegible] BIOSIS
DOCUMENT NUMBER: PREV[illegible]
TITLE: Polyunsaturated fatty acids and [illegible] the expression of the ATP-binding cassette transporter A1.

Search completed by David Schreiber [illegible]

Kam 09/9+2,544

AUTHOR S): Uehara, Yoshinari; Engel, Thomas; Li, Zhengchen; Goepfert, Christian; Rust, Stephan; Zhou, Xiaoqin; Langer, Claus; Schachtrup, Christian; Wiekowski, Johannes; Lorkowski, Stefan; Assmann, Gerd; von Eckardstein, Arnold (1)

CORPORATE SOURCE: (1) University Hospital Zurich, Institute of Clinical Chemistry, Rämistrasse 100, CH 8091, Zurich: arnold.voneckardstein@ikc.usz.ch Switzerland

SOURCE: Diabetes, (October, 2002) Vol. 51, No. 10, pp. 2922-2928. http://www.diabetes.org/Diabetes/. print. ISSN: 0012-1797.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Low HDL cholesterol is a frequent cardiovascular risk factor in diabetes. Because of its pivotal role for the regulation of HDL plasma levels, we investigated in vivo and in vitro regulation of the ATP-binding cassette transporter A1 (ABCA1) by insulin and metabolites accumulating in diabetes. Compared with euglycemic control mice, ABCA1 gene expression was severely decreased in the liver and peritoneal macrophages of **diabetic** mice. **Treatment** with insulin restored this deficit. Incubation of cultivated HepG2 hepatocytes and RAW264.7 macrophages with unsaturated fatty acids or acetoacetate, but not with insulin, glucose, saturated fatty acids, or hydroxybutyrate, downregulated ABCA1 mRNA and protein. The suppressive effect of unsaturated fatty acids and acetoacetate became most obvious in cells stimulated with oxysterols or retinoic acid but was independent of the expression of the thereby regulated transcription factors **liver-X-receptor** alpha (LXRalpha) and retinoid-X-receptor alpha (RXRalpha), respectively. Unsaturated fatty acids and acetoacetate also reduced ABCA1 promotor activity in RAW264.7 macrophages that were transfected with a 968-bp ABCA1 promotor/luciferase gene construct. As the functional consequence, unsaturated fatty acids and acetoacetate inhibited cholesterol efflux from macrophages. Downregulation of ABCA1 by unsaturated fatty acids and acetoacetate may contribute to low HDL cholesterol and increased cardiovascular risk of diabetic patients.

L35 ANSWER 11 OF 41 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002365386 EMBASE

TITLE: [Pharmacological **prevention** of **type 2 diabetes**]. APPROCHES PHARMACOLOGIQUES DE **PREVENTION** DU **DIABETE** DE **TYPE 2**.

AUTHOR: Scheen A.J.; Paquot N.; Letiexhe M.R.; Jandrain B.J.

CORPORATE SOURCE: A.J. Scheen, Serv. Diabet. Nutr./Malad. Metabol., Departement de Medecine, CHU Sart Tilman, 4000 Liege 1, Belgium. andre.scheen@chu.ulg.ac.be

SOURCE: Medecine et Hygiene, (28 Aug 2002) 60/2402 (1480-1484). Refs: 39 ISSN: 0025-8768 CODEN: MEHGAB

COUNTRY: Switzerland

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 003 Endocrinology
016 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
048 Adverse Reactions Titles

LANGUAGE: French

SUMMARY LANGUAGE: English; French

AB The rapidly increasing prevalence of type 2 diabetes requires the development of prevention strategies. Besides the essential lifestyle modifications, various pharmacological approaches have recently proven

Search completed by David Schreiber 308-4294

their efficacy in at risk subjects because of weight excess and/or impaired glucose tolerance. It is the case of several antidiabetic agents such as metformin, acarbose, or troglitazone. It is also the case of anti-obesity agents as orlistat and, perhaps, sibutramine. The inhibition of the renin-angiotensin system by an angiotensin converting enzyme inhibitor or by a selective AT1 receptor antagonist can also **prevent type 2 diabetes**, in addition to **reduce** the risk of **cardiovascular complications**. Finally, the role of hypolipidaemic drugs remains controversial. Ongoing prospective studies should confirm all these observations.

L35 ANSWER 12 OF 41 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2002350466 MEDLINE
DOCUMENT NUMBER: 22068265 PubMed ID: 12093315
TITLE: Metabolic and additional vascular effects of thiazolidinediones.
AUTHOR: Martens Fabrice M A C; Visseren Frank L J; Lemay Jacinthe; de Koning Eelco J P; Rabelink Ton J
CORPORATE SOURCE: Department of Internal Medicine, Section of Vascular Medicine and Diabetology, University Medical Center Utrecht, Room F.02.126, Heidelberglaan 100, PO Box 85500, 3508 GA Utrecht, The Netherlands.. F.M.A.C.Martens@azu.nl
SOURCE: DRUGS, (2002) 62 (10) 1463-80. Ref: 169
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020703
Last Updated on STN: 20020824
Entered Medline: 20020823

AB Several cardiovascular risk factors (dyslipidaemia, hypertension, glucose intolerance, hypercoagulability, obesity, hyperinsulinaemia and low-grade inflammation) cluster in the insulin resistance syndrome. Treatment of these individual risk factors reduces **cardiovascular complications**. However, targeting the underlying pathophysiological mechanisms of the insulin resistance syndrome is a more rational treatment strategy to further improve cardiovascular outcome. Our understanding of the so-called cardiovascular dysmetabolic syndrome has been improved by the discovery of nuclear peroxisome proliferator-activated receptors (PPARs). PPARs are ligand-activated transcription factors belonging to the nuclear receptor superfamily. As transcription factors, PPARs regulate the expression of numerous genes and affect glycaemic control, lipid metabolism, vascular tone and inflammation. Activation of the subtype PPAR-gamma improves insulin sensitivity. Expression of PPAR-gamma is present in several cell types involved in the process of atherosclerosis. Thus, modulation of PPAR-gamma activity is an interesting therapeutic approach to reduce cardiovascular events. Thiazolidinediones are PPAR-gamma agonists and constitute a new class of pharmacological agents for the **treatment** of **type 2** (non-insulin-dependent) **diabetes** mellitus. Two such compounds are currently available for clinical use: rosiglitazone and pioglitazone. Thiazolidinediones improve insulin sensitivity and glycaemic control in patients with type 2 diabetes. In addition, improvement in endothelial function, a decrease in inflammatory

conditions, a decrease in plasma levels of free fatty acids and lower blood pressure have been observed, which may have important beneficial effects on the vasculature. Several questions remain to be answered about PPAR-gamma agonists, particularly with respect to the role of PPAR-gamma in vascular pathophysiology. More needs to be known about the adverse effects of thiazolidinediones, such as hepatotoxicity, increased low-density lipoprotein cholesterol levels and increased oedema. The paradox of adipocyte differentiation with weight gain occurring with the insulin-sensitising effect of thiazolidinediones is not completely understood. The decrease in blood pressure induced by **thiazolidinedione** treatment seems incompatible with an increase in the plasma volume, and the discrepancy between the stimulation of the expression of CD36 and the antiatherogenic effects of the thiazolidinediones also needs further explanation. Long-term clinical trials of thiazolidinediones with cardiovascular endpoints are currently in progress. In conclusion, studying the effects of thiazolidinediones may shed more light on the mechanisms involved in the insulin resistance syndrome. Furthermore, thiazolidinediones could have specific, direct effects on processes involved in the development of vascular abnormalities.

L25 ANSWER 13 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7

ACCESSION NUMBER: 2003:644 BIOSIS
DOCUMENT NUMBER: PREV200300011644
TITLE: Novel roles of **liver X receptors** exposed by gene expression profiling in liver and adipose tissue.
AUTHOR(S): Stulnig, Thomas M. (1); Steffensen, Knut R.; Gao, Hui; Reimers, Mark; Dahlman-Wright, Karin; Schuster, Gertrud U.; Gustafsson, Jan-Ake
CORPORATE SOURCE: (1) Department of Internal Medicine III, Division of Endocrinology and Metabolism, University of Vienna, Waehringer Guertel 18-20, A-1090, Vienna, Austria: thomas.stulnig@akh-wien.ac.at Austria
SOURCE: Molecular Pharmacology, (December 2002, 2002) Vol. 62, No. 6, pp. 1289-1295. print.
ISSN: 0026-895X.
DOCUMENT TYPE: Article
LANGUAGE: English

AB **Liver X receptor** (**LXR**) alpha and LXRbeta are nuclear oxysterol receptors whose biological function has so far been elucidated only with respect to cholesterol and lipid metabolism. To expose novel biological roles for LXRs, we performed genome-wide gene expression profiling studies in liver and white and brown adipose tissue from wild-type (LXRalpha+/+ beta+/+) and knockout mice (LXRalpha-/- beta-/-) treated with a synthetic **LXR** agonist. By an adapted statistical analysis, we detected 319 genes significantly regulated by **LXR** agonist treatment in wild-type but not in knockout mice, fulfilling our stringent criteria with an overall confidence of 94 . Down-regulation of essential enzymes of gluconeogenesis in liver could point to possible beneficial effects of **LXR** agonists in **diabetes** mellitus. **LXR** agonist **treatment** also altered expression of genes involved in steroid hormone synthesis and growth hormone receptor signaling, emphasizing a potential impact in endocrine function. Notably, **LXR** agonist treatment up-regulated CYP8B1 and CYP4A14 together with cytochrome P450 reductase, indicating a possible enhancement of microsomal lipid peroxidation. In conclusion, tissue-wide expression profiling data identify novel areas of regulation by

LXRs and provide a highly valuable basis for further research on the biological functions of these nuclear receptors and the pharmacological characteristics of their ligands.

L35 ANSWER 14 OF 41 HCAPLUS COPYRIGHT 2013 ACS
ACCESSION NUMBER: 2002:27274 HCAPLUS
DOCUMENT NUMBER: 136:379867
TITLE: PPAR.gamma. is not a critical mediator of primary monocyte differentiation or foam cell formation
AUTHOR(S): Patel, Lisa; Charlton, Steven J.; Marshall, Ian C.; Moore, Gary B. T.; Coxon, Phil; Moores, Kitty; Clapham, John C.; Newman, Susanna J.; Smith, Stephen A.; Macphee, Colin H.
CORPORATE SOURCE: Department of Vascular Biology, GlaxoSmithKline, Harlow, Essex, CM19 5AW, UK
SOURCE: Biochemical and Biophysical Research Communications (2002), 290(2), 707-712
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present report we clarify the role of PPAR.gamma. in differentiation and function of human-derived monocyte/macrophages in vitro. Rosiglitazone, a selective PPAR.gamma. activator, had no effect on the kinetics of appearance of monocyte/macrophage differentiation markers or on cell size or granularity. Depletion of PPAR.gamma. by more than 90% using antisense oligonucleotides did not influence accumulation of oxidized LDL or prevent the upregulation of CD36 that normally accompanies oxLDL treatment. In contrast, PPAR.gamma. depletion reduced the expression of ABCA1 and **LXR**.alpha. mRNAs. Metalloproteinase-9 expression, a marker of atherosclerotic plaque vulnerability, was suppressed by rosiglitazone. We conclude that activation of PPAR.gamma. does not affect monocyte/macrophage differentiation. In addn., PPAR.gamma. is not absolutely required for oxLDL-driven lipid accumulation, but is required for full expression of ABCA1 and **LXR** .alpha.. Our data support a role for rosiglitazone as a potential directly acting antiatherosclerotic agent. (c) 2002 Academic Press.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 15 OF 41 HCAPLUS COPYRIGHT 2013 ACS
ACCESSION NUMBER: 2002:275509 HCAPLUS
DOCUMENT NUMBER: 137:163105
TITLE: Recent developments of retinoids as therapeutic agents
AUTHOR(S): Hu, Shi-Yong
CORPORATE SOURCE: Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Expert Opinion on Therapeutic Patents (2002), 12(4), 523-542
CODEN: EOTPEC; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Retinoids, a group of natural and synthetic retinol (vitamin A) analogs, play an important role in regulating pleiotropic biol. events, including growth, differentiation and death of normal, premalignant and malignant cell types, which appears to account for their therapeutic [illegible] promising activity in acne, psoriasis, [illegible]

diseases. Nuclear retinoic acid receptors and retinoid X receptors are thought to mediate the majority of retinoid biol. effects. One effective strategy is to design and synthesize retinoids with receptor selectivity restricted to specific retinoic acid receptors or retinoid X receptor subtypes (.alpha., .beta. and .gamma.) to develop novel retinoids with a more favorable therapeutic index and with reduced adverse effects and teratogenic risk. Indeed, retinoid medicinal chem. has identified ligands that include highly specific antagonists for one of the three RAR subtypes and for retinoid X receptors. Since the retinoid X receptors also serve as heterodimer partners for several other nuclear receptors, including thyroid hormone receptors, vitamin D **receptors**, peroxisomal proliferator-activator **receptors**, Farnesoid **X receptors** and **liver X receptors**, retinoid **X receptor**-selective retinoids may have clin. applications for the prevention and treatment of diseases other than dermatol. diseases and cancer, such as diabetes, obesity and atherosclerosis.

REFERENCE COUNT: 109 THERE ARE 109 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 16 OF 41 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 20030611237 MEDLINE
DOCUMENT NUMBER: 22414146 PubMed ID: 12537363
TITLE: [Thiazolidinediones in type 2 diabetes. Role of peroxisome proliferator-activated receptor gamma (PPARgamma)]. Thiazolidinediones dans le diabete de type 2. Role du peroxisome proliferator-activated receptor gamma (PPARgamma).
AUTHOR: Dubois M; Vantyghem M-C; Schoonjans K; Pattou F
CORPORATE SOURCE: EBIM 1166, Therapie Cellulaire du Diabete, Faculte de Medecine, 1, place de Verdun, 59045 Lille Cedex.
SOURCE: ANNALES D ENDOCRINOLOGIE, (2002 Dec) 63 (6 Pt 1) 511-23. Ref: 106
Journal code: 0114744. ISSN: 0003-4266.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030321
Last Updated on STN: 20030326
Entered Medline: 20030325

AB Thiazolidinediones (TZDs) form a new class of oral antidiabetic agents. They improve insulin sensitivity and reduce glycemia, lipidemia and insulinemia in patients with type 2 diabetes. Their mechanism is original, since they activate the nuclear receptor Peroxisome Proliferator-Activated Receptor gamma (PPARgamma), altering the expression of genes involved in glucose and lipid homeostasis. Stimulating PPARgamma improves insulin sensitivity via several mechanisms: 1) it raises the expression of GLUT4 glucose transporter; 2) it regulates release of adipocyte-derived signaling factors that affect insulin sensitivity in muscle, and 3) it contributes to a turn-over in adipose tissue, inducing the proliferation of smaller, more insulin sensitive adipocytes. TZDs also affect free fatty acids (FFA) lipotoxicity on islets, improving pancreatic B-cell function. In addition, triglycerides and FFA levels are lowered by TZDs. Two TZDs, rosiglitazone and pioglitazone, have recently obtained

the European commercial licence, but their use is restricted to the association with metformin or sulfonylureas. At the moment, they are indicated in type 2 diabetes but could be of interest in a broader array of diseases related to insulin resistance. As for side effects, rosiglitazone and pioglitazone may cause increased plasma volume, edema and a moderate weight gain. TZDs offer an attractive option in the **treatment** of **type 2 diabetes**, though it may be too soon to determine if they prevent **vascular complications**, as do other oral antidiabetic agents. An important issue for the future will be to assess the influence of weight gain in the long time.

L35 ANSWER 17 OF 41 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002356659 EMBASE
TITLE: [Type 2 diabetes mellitus: Should be diagnosed and treated as a cardiovascular disease?].
LA DIABETES TIPO 2 DEBERIA DIAGNOSTICARSE Y TRATARSE COMO UNA ENFERMEDAD CARDIOVASCULAR?.
AUTHOR: Millaruelo Trillo J.M.; Sangros Gonzalez J.; Romero Serrano F.
CORPORATE SOURCE: J.M. Millaruelo Trillo, Centro de Salud Torrero La Paz, C/ Soleiman 11, 50007 Zaragoza, Spain. jmmillaruelo@able.es
SOURCE: MEDIFAM - Revista de Medicina Familiar y Comunitaria, (2002) 12/8 (508-514).
Refs: 30
ISSN: 1131-6763 CODEN: RMFCF3
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
016 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: Spanish
SUMMARY LANGUAGE: English; Spanish
AB There are an increasing body of evidences from clinical trials that associate type 2 diabetes with cardiovascular disease, especially since the majority of those patients die from a **cardiovascular** disease and macrovascular **complications**. Recent prospective studies have shown that achieving a good metabolic control by decreasing fasting plasma glucose and glycosylated hemoglobin is possible to prevent the development of microvascular complications of type 2 diabetics. Nevertheless, other epidemiological studies have stressed the importance of postprandial hyperglycemia and his role as an independent risk factor of cardiovascular morbidity and mortality. People affected by the so-called metabolic syndrome (hypertension, dyslipidemia, central adiposity, insulin resistance and hyperinsulinism) have a high risk to develop a cardiovascular disease, even without been affected by type 2 diabetes but only with impaired glucose tolerance. This showing that the cardiovascular risk is increasing at the same time as the entire glycemic levels (both mealtime glucose spikes and fasting plasma glucose). The current therapeutical choices to correct the metabolic alterations of diabetes should also prevent the appearance of long-term macrovascular complications of the disease. Nateglinide, a rapid-onset, short-acting insulin secretion enhancer, which acts to effectively reduce mealtime glucose spikes, could offer a good **therapeutical** option to manage patients with **type 2 diabetes**.

L35 ANSWER 18 OF 41 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 22126487[illegible] MEDLINE
DOCUMENT NUMBER: [illegible] PubMed ID: [illegible]

[illegible]

Kam 09/982,544

TITLE: Effects of thiazolidinediones for early **treatment** of **type 2 diabetes** mellitus.
AUTHOR: Kudema David J
CORPORATE SOURCE: United Healthcare of Florida, Sunrise, USA.
SOURCE: AMERICAN JOURNAL OF MANAGED CARE, (2002 Oct) 8 (16 Suppl) S472-81. Ref: 61
Journal code: 9613960. ISSN: 1096-1860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Health
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021105
Last Updated on STN: 20021214
Entered Medline: 20021126

AB The thiazolidinediones (TZDs) are a new class of oral antidiabetic agents used in the **treatment** of **type 2 diabetes** mellitus. TZDs are selective and potent agonists of peroxisome proliferator-activated receptor-gamma, which is expressed in target tissues for insulin action and in a variety of cells that play an important role in atherosclerosis. TZDs primarily improve glycemic control by reducing insulin resistance in target tissues. Evidence also suggests that the TZDs may have a direct, beneficial effect on beta-cell function. In patients with impaired glucose tolerance (prediabetics), treatment with a TZD improves insulin secretory responses and proinsulin concentrations. These beta-cell-specific effects may result in prolongation of beta-cell function and the enduring glycemic control necessary to prevent microvascular complications. Durable glycemic control has not been clearly demonstrated with other antihyperglycemic agents. The TZDs may prevent or delay the macrovascular complications associated with type 2 diabetes. TZDs improve the characteristic dyslipidemia of **type 2 diabetes**, promote **decreases** in blood pressure, and enhance fibrinolysis. In addition, they exert direct effects on the vasculature, including the ability to decrease the intimal medial thickness and inhibit transendothelial migration of monocytes. These demonstrated antiatherogenic effects may reduce the **cardiovascular complications** commonly associated with type 2 diabetes. TZDs also reduce microalbuminuria to a greater extent than other agents. Use of a TZD early in the course of therapy may reduce the risk of development of many of the long-term microvascular and macrovascular complications associated with type 2 diabetes.

L35 ANSWER 19 OF 41 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002347467 EMBASE
TITLE: Molecular mechanisms leading to the development of diabetes.
AUTHOR: Parrizas M.
CORPORATE SOURCE: Dr. M. Parrizas, Department of Endocrinology, Hospital Clinic i Provincial, Villarroel 170, esc. 11, pl.2, Barcelona 08036, Spain. parrinas@clinic.ub.es
SOURCE: Drug News and Perspectives, (2002) 15(6) [333-350].
Refs: 82
ISSN: 0214-9934 CODEN: DNPEED
COUNTRY: Spain
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 End Endocrinology

Search completed by David Schreiber 308-4290

030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Current **therapy** for **type 2 diabetes** relies mainly on several approaches intended to reduce hyperglycemia. Several major studies have shown that the appropriate longterm management of glycemia is critical to reduce the risk of **vascular complications**. Thus, the goal of future treatments of the disease will be to intervene when early clinical signs, such as impaired glucose tolerance, first manifest and to exploit the knowledge of the molecular mechanisms of insulin secretion by the .beta.-cells as well as insulin action in its target tissues to develop new drugs to accomplish a tight glycemic control. . COPYRGT. 2002 Prous Science. All rights reserved.

L35 ANSWER 20 OF 41 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2002:474764 SCISEARCH
THE GENUINE ARTICLE: 557VB
TITLE: Roles of peroxisome proliferator-activated receptor gamma in lipid homeostasis and inflammatory responses of macrophages
AUTHOR: Klappacher G W; Glass C K (Reprint)
CORPORATE SOURCE: Univ Calif San Diego, Dept Cellular & Mol Med, 9500 Gilman Dr, La Jolla, CA 92093 USA (Reprint); Univ Calif San Diego, Dept Cellular & Mol Med, La Jolla, CA 92093 USA; Univ Vienna, Dept Cardiol, Vienna, Austria
COUNTRY OF AUTHOR: USA; Austria
SOURCE: CURRENT OPINION IN LIPIDOLOGY, (JUN 2002) Vol. 13, No. 3, pp. 305-311.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0957-9672.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 64
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Monocytes play a critical role in atherogenesis by their inflammatory signals and differentiation into macrophage foam cells through cholesterol accumulation. The seminal finding of high levels of the peroxisome proliferator-activated receptor gamma in macrophage foam cells has opened up the prospect that its ligands, most importantly the **thiazolidinedione** class of drugs, might directly influence the development of atheromatous lesions. The present review weighs the growing evidence on regulation of both inflammatory responses and cholesterol homeostasis in macrophages by peroxisome proliferator-activated receptor gamma liganos with regard to their overall impact as antiatherogenic agents. Curr Opin Lipidol 13:305-312. (C) 2002 Lippincott Williams Wilkins.

L35 ANSWER 21 OF 41 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002241814 EMBASE
TITLE: Lipid metabolism regulation by nuclear receptors.
AUTHOR: Kwiatkowska D.; Kwiatkowska-Korczak J.
CORPORATE SOURCE: D. Kwiatkowska, Katedra Zaklad Biochem Lekarskiej AM, ul. Chalubinskiego 10, 50-368 Wroclaw, Poland
SOURCE: Advances in Clinical and Experimental Medicine, (2002) 11/2 (217-228).
Refs: 46

Kam 09/982,044

ISSN: 1230-025X CODEN: ACEMC6
COUNTRY: Poland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 019 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Synthesis of enzymes and other proteins, involved in lipid metabolism is regulated by heterodimeric receptors: peroxisome proliferator receptors (PPAR(.alpha.), PPAR(.gamma.), PPAR(.delta.)), **liver X receptors** (**LXR**) and farnesoid **X receptors** (FXR). Activated **receptors** bind regulatory elements of DNA and regulate transcription of target genes. PPARs are activated by fatty acids and eicosanoids, antidiabetic drugs and drugs decreasing lipid concentration in serum. PPAR(.alpha.) stimulates lipid transport and metabolism in liver and gut. Obesity, hyperlipidemia and disturbances of tissue lipid metabolism are often accompanied by decreased PPAR.alpha. activity. Fibrates, high-affinity ligands of the receptor are used in these diseases successfully. PPAR(.gamma.) and PPAR(.delta.) stimulate adipocyte differentiation and metabolism of adipose tissue. Synthetic ligands, thiazolidinediones (TZD) are known to **decrease insulin resistance, hyperglycemia** and hyperlipidemia. **LXR** binds oxidized cholesterol derivatives, stimulates cholesterol transport and bile acids synthesis. FXR activated by bile acids inhibits their synthesis.

L15 ANSWER 22 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:13264 BIOSIS
DOCUMENT NUMBER: PREV200300013264
TITLE: Challenges in optimal metabolic control of diabetes.
AUTHOR(S): Liebl, Andreas (1)
CORPORATE SOURCE: (1) Diabetes Zentrum Bosswandweg, Bottach-Egern, 83700, Germany: dr.liebl@t-online.de Germany
SOURCE: Diabetes-Metabolism Research and Reviews, (September October 2002) Vol. 18, No. Suppl. 3, pp. S36-S41. print. ISSN: 1520-7552.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The results of the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) showed that tight glycemic control with any of several therapeutic regiments has the potential to significantly reduce the risks for long-term microvascular complications of type 1 or type 2 diabetes. The results of these large-scale long-term studies also demonstrated that there is no threshold for the relationship between blood glucose (i.e. glycosylated hemoglobin (HbA1c)) and reduced risk. This means that 'optimal' glycemic control in a patient with type 1 or type 2 diabetes is a blood glucose level as close as possible to the level in an individual without **diabetes**. Limitations of most available **therapies** for **type 1** and **2 diabetes** have hampered achievement of this goal. Most available insulin preparations used to treat patients with type 1 disease can achieve approximately normal basal insulin levels only when used with a pump or a complex treatment regimen requiring a large number of daily injections. Pumps are limited by high expense, and complex injection protocols increase the potential for patient errors and non-compliance. The development of new insulins such as aspart insulin and lispro insulin, both short-acting, and insulin glargine, a long-acting insulin analogue suitable for once-daily administration, may help overcome these

challenges. In patients with type 2 diabetes, achieving optimal glycemic control is complicated by the progressive nature of the disease and the loss of efficacy of oral agents (e.g. sulfonylureas, metformin, and thiazolidinediones) over time. Moreover, neither oral therapy nor insulin alone is likely to achieve optimal glycemic control in most of these patients in the long term. The availability of new insulin preparations that mimic the normal mealtime bursts of insulin, and another that provides a sustained insulin supply similar to basal insulin secretion in an individual without diabetes has the potential to significantly improve long-term control over blood glucose in patients with type 2 diabetes.

L35 ANSWER 33 OF 41 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2002:472409 SCISEARCH
THE GENUINE ARTICLE: 557HB
TITLE: Is a new therapeutic class justified in the **treatment** of **type 2 diabetes**?
AUTHOR: Halimi S (Reprint)
CORPORATE SOURCE: CHU Grenoble, Serv Endocrinol, F-38043 Grenoble, France (Reprint)
COUNTRY OF AUTHOR: France
SOURCE: ANNALES D ENDOCRINOLOGIE, (APR 2002) Vol. 63, No. 2, Part 2, pp. S7-S11.
Publisher: MASSON EDITEUR, 120 BLVD SAINT-GERMAIN, 75280 PARIS 06, FRANCE.
ISSN: 0003-4266.
DOCUMENT TYPE: Article; Journal
LANGUAGE: French
REFERENCE COUNT: 15

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Type 2 diabetes is responsible for various micro and macro-**vascular complications**, appearing early in the course of the disease. The UKPDS results clearly demonstrate the interest of an early and intensive treatment of hyperglycaemia to reduce theses microvascular complications and, to a lesser extent, macrovascular complications. The UKPDS also demonstrate the limits of the current management of type 2 diabetes: delayed diagnosis when several complications already exist, difficulties to maintain an adequate glucose control over the time, particularly with monotherapy, need for an intensive combination treatment policy, unwanted effects of this intensive treatment (weight gain, hypoglycaemias). The 3 classes of oral anticiabetic agents currently available (sulfonylureas and meteglinide analogues, metformin, alpha-glucosidase inhibitors) imperfectly cover the current therapeutic needs. Thus, the new class, the thiazolidinediones, acting on key physiopathological components, appears as a welcome addition to the **treatment** of **type 2 diabetes**. The association of metformin (or a sulfonylurea) and a **thiazolidinedione** should permit to obtain early a better glycaemic control without the hypoglycaemic risk associated with intensive **therapy** at an early stage of **type 2 diabetes**.

L35 ANSWER [illegible] OF 41 MEDLINE DUPLICATE 10
ACCESSION NUMBER: [illegible] MEDLINE
DOCUMENT NUMBER: [illegible] PubMed ID: [illegible]
TITLE: Is a new therapeutic class justified in the **treatment** of **type 2 diabetes**?
[illegible]

[illegible]

Ram. 09/982,544

le traitement du diabete de type 2?.
AUTHOR: Halimi S
CORPORATE SOURCE: Service d'Endocrinologie - Diabetologie - Nutrition, CHU de Grenoble, F - 38043 Grenoble Cedex, France.
SOURCE: ANNALES D ENDOCRINOLOGIE, (2002 Apr) 63 (2 Pt 2) 1S7-11. Ref: 19
Journal code: 0116744. ISSN: 0003-4266.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
REVIEW, TUTORIAL
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020731
Last Updated on STN: 20020801
Entered Medline: 20020731

AB Type 2 diabetes is responsible for various micro and macro-**vascular complications**, appearing early in the course of the disease. The UKPDS results clearly demonstrate the interest of an early and intensive treatment of hyperglycaemia to reduce theses microvascular complications and, to a lesser extent, macrovascular complications. The UKPDS also demonstrate the limits of the current management of type 2 diabetes: delayed diagnosis when several complications already exist, difficulties to maintain an adequate glucose control over the time, particularly with monotherapy, need for an intensive combination treatment policy, unwanted effects of this intensive treatment (weight gain, hypoglycaemias). The 3 classes of oral antidiabetic agents currently available (sulfonylureas and meteglinide analogues, metformin, a-glucosidase inhibitors) imperfectly cover the current therapeutic needs. Thus, the new class, the thiazolidinediones, acting on key physiopathological components, appears as a welcome addition to the **treatment** of **type 2 diabetes**. The association of metformin (or a sulfonylurea) and a **thiazolidinedione** should permit to obtain early a better glycaemic control without the hypoglycaemic risk associated with intensive **therapy** at an early stage of **type 2 diabetes**.

L15 ANSWER 25 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:72660 BIOSIS
DOCUMENT NUMBER: PREV200300172660
TITLE: Identification of **Liver X Receptors** as endogenous inhibitors of atherosclerosis.
AUTHOR(S): **Tangirala, Rajendra K. (1); Bischoff, Eric D. (1)**; Joseph, Sean B.; Wagner, Brandee L. (1); Walczak, Robert; Laffitte, Bryan A.; Daige, Chris L. (1); Thomas, Diane (1); Heyman, Richard A. (1); Mangelsdorf, David J.; Wang, Xuping; Lusis, Aldons J.; Tontonoz, Peter; **Schulman, Ira G. (1)**
CORPORATE SOURCE: (1) X-Ceptor Therapeutics Inc, San Diego, CA, USA USA
SOURCE: Circulation, (November 5 2002) Vol. 106, No. 19 Supplement, pp. II-73. print.
Meeting Info.: Abstracts from Scientific Sessions Chicago, IL, USA November 17-20, 2002 American Heart Association . ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

Search completed by David Schreiber 308-4292

L35 ANSWER 26 OF 41 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:816448 HCAPLUS
DOCUMENT NUMBER: 135:352751
TITLE: Treatment of hypertriglyceridemia and other conditions using nuclear receptor **LXR** modulators
INVENTOR(S): Shan, Bei; Schultz, Joshua; Tu, Hua
PATENT ASSIGNEE(S): Tularik Inc., USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001081310	A2	20011108	WO 2001-US14586	20010503
WO 2001081310	A3	20020606		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 20020048572	A1	20020425	US 2001-848990	20010503
PRIORITY APPLN. INFO.:			US 2000-201601P P	20000503

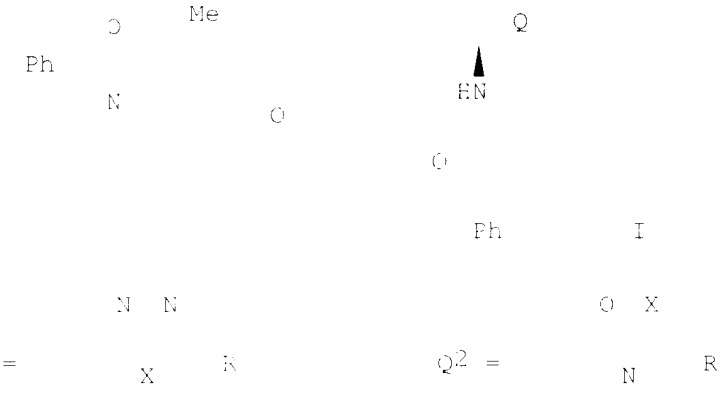
AB This invention provides methods for identifying compds. that are suitable for use in modulating fatty acid and triglyceride biosynthesis, and thus treating conditions such as hypertriglyceridemia and lipodystrophy, among others. Provided are in vitro assays by which one can conduct prescreening to identify candidate therapeutic agents that are suitable for further testing, as well as assays for identifying agents that are useful for administration for treating conditions assocd. with abnormalities in fatty acid and triglyceride biosynthesis.

L35 ANSWER 27 OF 41 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:135780 HCAPLUS
DOCUMENT NUMBER: 134:167479
TITLE: Preparation of 5-methyl-4-phenoxyethyl-2-phenyloxazoles as PPAR, FXR, **LXR**-.alpha., or **LXR**-.beta. antagonists
INVENTOR(S): Cobb, Jeffrey Edmond; Lambert, Millard Hurst, III; Milburn, Michael Vance; Shearer, Barry George
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012614	A1	20010222	WO 2000-IB1144	20000811

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1210345 A1 20020605 EP 2000-959913 20000801
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL
JP 2003508529 T2 20030304 JP 2001-522217 20000811
US 6506781 B1 20030114 US 2002-70474 20020307
PRIORITY APPLN. INFO.: US 1999-152761P P 19990908
US 2000-199969P P 20000427
WO 2000-US24364 W 20000811
OTHER SOURCE(S): MARPAT 134:237473
RE



AB Title compds. (I; Q = Q1, Q2; X = O, S, NH; R = Me, Et, Pr, Me2CH, cyclopropyl, Bu, PH, MeOCH2; X1 = C, N; R1 = Me, Et, Pr, Me2CH, MeOCH2, CO2Me), were prepd. A method is disclosed for rational design of a PPAR, FXR, **LXR**-.alpha., or **LXR**-.beta. antagonist comprising chem. modification of a PPAR, FXR, **LXR**-.alpha., or **LXR**-.beta. agonist to: (a) prevent formation of a hydrogen bond between the agonist and tyrosine, histidine, or tryptophan involved in receptor activation; and/or (b) displace the tyrosine, histidine, or tryptophan involved in receptor activation from its agonist bound position. Preferably, few or no addnl. changes are made in the structure of the agonist so that the resulting antagonist is a close structural analog of the agonist. Thus, (2S)-[(2-benzoylphenyl)amino]-3-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]propionic acid in THF was treated with 4-methylmorpholine and iso-Bu chloroformate; the mixt. was stirred 30 min, filtered, and added to a soln. of N2H4 in THF to give the propionic hydrazide, which was heated with tri-Me orthobutyrate and MeSO3H in dioxane at 100.degree. for 15 min. to give 84% (5S)-[(2-[1-(2-benzoylphenyl)amino]-2-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]ethyl]-5-propyl-1,3,4-oxadiazole. I showed >50% inhibition of transactivation by 100 nM rosiglitazone in a PPAR-.gamma.

cell based reporter assay.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 19 OF 41 SCISEARCH COPYRIGHT © 1 TS THOMSON ISI
ACCESSION NUMBER: 2001:916172 SCISEARCH
THE GENUINE ARTICLE: 496WH
TITLE: Novel agents for managing dyslipidaemia
AUTHOR: Best J D (Reprint); Jenkins A J
CORPORATE SOURCE: Univ Melbourne, St Vincent Hosp, Dept Med, Fitzroy, Vic 3065, Australia (Reprint)
COUNTRY OF AUTHOR: Australia
SOURCE: EXPERT OPINION ON INVESTIGATIONAL DRUGS, (NOV 2001) V 1. 10, No. 11, pp. 1901-1911.
Publisher: ASHLEY PUBLICATIONS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT PLACE FINCHLEY CENTRAL, LONDON N3 1QB, ENGLAND.
ISSN: 1354-3784.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 100
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB An elevated low-density lipoprotein (LDL) cholesterol level is a strong predictor of coronary heart disease (CHD) risk. Over the past seven years, equally strong evidence has accumulated that lowering LDL cholesterol with HMG-CoA reductase inhibitors or statins reduces CHD risk and there is now widespread use of these agents for the primary and secondary prevention of CHD. Treatment issues remain regarding the appropriate degree of LDL cholesterol reduction and whether, in people with very high levels, it would be preferable to achieve the LDL cholesterol goal with a powerful statin alone or combined with an agent that lowers LDL cholesterol by a different mechanism. The main focus in the development of novel agents is the patient with low high-density lipoprotein (HDL) cholesterol, usually associated with hypertriglyceridaemia. Already prevalent as a risk factor for CHD, this abnormality has been linked with insulin resistance, which is likely to increase greatly over the next decade, along with increasing obesity and **diabetes**. Agents that have potent HDL cholesterol raising capacity include cholesteryl ester transfer protein (CETP) inhibitors, retinoid X receptor (RXR) selective agonists, specific peroxisome proliferator-activated receptor (PPAR) agonists and oestrogen-like compounds. Another area of development involves agents that will lower both cholesterol and triglyceride levels, such as partial inhibitors of microsomal triglyceride transfer protein (MTP) and perhaps squalene synthase inhibitors and agonists of AMP kinase. Future emphasis will be on correcting all lipid abnormalities for the prevention of CHD, not just lowering LDL cholesterol.

L37 ANSWER 20 OF 41 MEDLINE
ACCESSION NUMBER: 2001414593 MEDLINE
DOCUMENT NUMBER: 21357001 PubMed ID: 11468868
TITLE: The rexinoid LG100754 is a novel RXR:PPARgamma agonist and decreases glucose levels in vivo.
AUTHOR: Cesario R M; Klausing K; Razzaghi H; Crombie D; Kumar R; Heyman R A; Lala D S
CORPORATE AUTHOR: Department of Nuclear Receptor Research, Ligand Pharmaceuticals, Inc., San Diego, California 92121, USA.
SOURCE: MOLECULAR ENDOCRINOLOGY, [illegible]
Journal code: [illegible]. ISSN: [illegible].
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; JOURNAL ARTICLE

Search completed by David Schreiber [illegible]

Kam 09/896,144

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20011001
Entered Medline: 20010927

AB The RXR serves as a heterodimer partner for the PPARgamma and the dimer is a molecular target for insulin sensitizers such as the thiazolidinediones. Ligands for either receptor can activate PPAR-dependent pathways via PPAR response elements. Unlike PPARgamma agonists, however, RXR agonists like LG100268 are promiscuous and activate multiple RXR heterodimers. Here, we demonstrate that LG100754, a RXR:RXR antagonist and RXR:PPARalpha agonist, also functions as a RXR:PPARgamma agonist. It does not activate other LG100268 responsive heterodimers like RXR:**liver X** receptoralpha, RXR:**liver X** receptorbeta, RXR:bile acid **receptor**/farnesoid X receptor and RXR:nerve growth factor induced gene B. This unique RXR ligand triggers cellular RXR:PPARgamma-dependent pathways including adipocyte differentiation and inhibition of TNFalpha-mediated hypophosphorylation of the insulin receptor, but does not activate key farnesoid **X receptor** and **liver X receptor** target genes. Also, LG100754 treatment of db/db animals leads to an improvement in insulin resistance in vivo. Interestingly, activation of RXR:PPARgamma by LG100268 and LG100754 occurs through different mechanisms. Therefore, LG100754 represents a novel class of insulin sensitizers that functions through RXR but exhibits greater heterodimer selectivity compared with LG100268. These results establish an approach to the design of novel RXR-based insulin sensitizers with greater specificity.

L35 ANSWER 30 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:570939 BIOSIS
DOCUMENT NUMBER: PREV200100570939
TITLE: Insulin **therapy** in **type 2** **diabetes**.
AUTHOR(S): Muduliar, Sunder; Edelman, Steven V. (1)
CORPORATE SOURCE: (1) VA San Diego HealthCare System, 3350 La Jolla Village Drive, San Diego, CA, 92161: svedelman@vapop.ucsd.edu USA
SOURCE: Endocrinology and Metabolism Clinics of North America, (December, 2001) Vol. 30, No. 4, pp. 935-962. print.
ISSN: 0889-8529.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English

L35 ANSWER 31 OF 41 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 2002030020 MEDLINE
DOCUMENT NUMBER: 21594510 PubMed ID: 11735645
TITLE: Hepatotoxicity with thiazolidinediones: is it a class effect?.
AUTHOR: Schoen A J
CORPORATE SOURCE: Department of Medicine, CHU Sart Tilman, Liege, Belgium.. Andre.Schoen@chu.ulg.ac.be
SOURCE: DRUG SAFETY, (2001) 24 (12) 873-88. Ref: 138
Journal code: [illegible]. ISSN: 1114-5915.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; JOURNAL ARTICLE
General Review; REVIEW
REVIEW, TUTORIAL
LANGUAGE: English

Search completed by [illegible]

Kam 09/982,144

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020124
Last Updated on STN: 20030318
Entered Medline: 20020402

AB Decreased insulin sensitivity plays a major role in various human diseases, particularly type 2 diabetes mellitus, and is associated with a higher risk of atherosclerosis and **cardiovascular complications**. Thiazolidinediones, more commonly termed glitazones, are the first drugs to specifically target muscular insulin resistance. They have proven efficacy for reducing plasma glucose levels in patients with **type 2 diabetes** mellitus **treated** with diet alone, sulphonylureas, metformin or insulin. In addition, they are associated with some improvement of the cardiovascular risk profile. However, troglitazone, the first compound approved by the Food and Drug Administration in the US, proved to be hepatotoxic and was withdrawn from the market after the report of several dozen deaths or cases of severe hepatic failure requiring liver transplantation. It remains unclear whether or not hepatotoxicity is a class effect or is related to unique properties of troglitazone. Rosiglitazone and pioglitazone, two other glitazones, appear to have similar efficacy with regard to blood glucose control in patients with type 2 diabetes mellitus as compared with troglitazone. In controlled clinical trials, the incidence of significant (>3 x upper limit of normal) increases in liver enzyme levels (ALT in particular) was similar with rosiglitazone or pioglitazone as compared with placebo, whereas troglitazone was associated with a 3-fold greater incidence. In contrast to the numerous case reports of acute liver failure in patients receiving troglitazone, only a few case reports of hepatotoxicity have been reported in patients treated with rosiglitazone until now, with a causal relationship remaining uncertain. Furthermore, no single case of severe hepatotoxicity has been reported yet with pioglitazone. It should be mentioned that troglitazone, unlike pioglitazone and rosiglitazone, induces the cytochrome P450 isoform 3A4, which is partly responsible for its metabolism, and may be prone to drug interactions. Importantly enough, obesity, insulin resistance and type 2 diabetes mellitus are associated with liver abnormalities, especially non-alcoholic steatohepatitis, independent of any pharmacological treatment. This association obviously complicates the selection of patients who are good candidates for a treatment with glitazones as well as the monitoring of liver tests after initiation of therapy with any **thiazolidinedione** compound. While regular monitoring of liver enzymes is still recommended and more long term data are desirable, current evidence from clinical trials and postmarketing experience in the US supports the conclusion that rosiglitazone and pioglitazone do not share the hepatotoxic profile of troglitazone.

L35 ANSWER 32 OF 41 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002071233 EMBASE
TITLE: Review: Current trends and new approaches in the management of diabetes mellitus.
AUTHOR: Kao P.C.; Wu T.-C.; Ho L.L.-T.; Li K.C.
CORPORATE SOURCE: Dr. P.C. Kao, Dept. of Lab. Medicine and Pathology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. kao.pai@mayo.edu
SOURCE: Annals of Clinical and Laboratory Science, (2002) 32/4 (339-345).
Refs: 49
ISSN: 0091-7370 CODEN: ACLSCP
COUNTRY: United States

Search completed by David Schreiber 308-4292

Kam 09/982,144

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Current trends in the management of type 2 diabetes mellitus, based on the 20-year United Kingdom Prospective Diabetic Study, include intensive treatment to control the blood glucose level and blood pressure in order to prevent or delay microvascular and **cardiovascular complications**. In the new millennium, type 2 diabetes will become epidemic in developing countries. If diabetes were to develop in 10 of the 1.2 billion population of China, the expense of intensive treatment would be immense. Laboratory tests are useful for detecting risk factors before the onset of the disease and convincing the general public to take preventive measures. Glucose tolerance testing is one of these tests. When glucose tolerance is impaired, 25 of .beta.-cell function is lost. Determining the plasma proinsulin level is another useful evaluation; impaired glucose tolerance accompanied by increased plasma proinsulin level is indicative of an enhanced risk that type 2 diabetes will develop within 5 years. Educating the public about eating a healthy diet and exercising may prevent the development of **diabetes** and thereby **reduce** the global prevalence of **type 2 diabetes**.

L35 ANSWER 33 OF 41 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:641103 HCAPLUS
DOCUMENT NUMBER: 134:13034
TITLE: Clinical efficacy of new thiazolidinediones and glinides in the **treatment** of **type 2 diabetes** mellitus
AUTHOR(S): Buchenbusch, Martin; Standl, Eberhard; Schatz, Helmut
CORPORATE SOURCE: Diabetes Research Institute and 3rd Medical Department, Academic Hospital Munchen-Schwabing, Munich, Germany
SOURCE: Experimental and Clinical Endocrinology & Diabetes (2000), 108(3), 151-167
CODEN: ECEDEQ; ISSN: 0947-7349
PUBLISHER: Johann Ambrosius Barth
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 50 refs. A central finding of the UKPDS was that in type 2 diabetic patients, tight glycemic control with HbA1c targets as close to the normal range as possible must be achieved to further reduce diabetes related-**complications**, -mortality, and -**cardiovascular** disease, highlighting the need for new, optimized treatment strategies. With a focus on clin. efficacy, this paper discusses the results from the 20 major therapeutical trials published in the years 1997-1999, that evaluated the new insulin-sensitizing thiazolidinediones Rosiglitazone and Pioglitazone and the new insulin-releasing potassium channel blockers Repaglinide and Nateglinide. While for Nateglinide, promising, but only preliminary data is available at current, Rosiglitazone, Pioglitazone, and Repaglinide have been shown appropriate for both mono- and combination therapy with current std. drug **treatment** of **type 2 diabetes**. Similar to the known, older antidiabetic drugs, the new agents discussed have comparable blood glucose lowering potentials with a dose-related capacity of 1.5 to 1.5 HbA1c redn. These beneficial effects were both seen in drug-naive patients previously treated with diet only and in combination therapies where patients had

Search completed by David Schreiber 308-4291

previous antidiabetic std. drug treatment suggesting effectiveness of glitazones and glinides also in more advanced stages of the disease. Problems with adverse effects appeared minor although longer-range implications of wt. gain, edema, lowering of Hb, increase of total cholesterol for the glitazones, and hypoglycemia for glinides warrant further consideration. What becomes clear from the variety of most recent mono- and combination treatment studies with as much as five different classes of antidiabetic drugs is that individually tailored therapies that recognize quality of life parameters and target the predominant features of metabolic pathol. (such as early postprandial vs. fasting hyperglycemia, degree of insulin resistance, progressive loss of .beta.-cell function) may become a feasible goal in the future.
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 34 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:501884 BIOSIS
DOCUMENT NUMBER: PREV200061501884
TITLE: Clinical efficacy of new thiazolidinediones and glinides in the **treatment** of **type 2 diabetes** mellitus.
AUTHOR(S): Fuechtenbusch, Martin; Standl, Eberhard (1); Schatz, Helmut
CORPORATE SOURCE: (1) 3rd Medical Department, Diabetes Research Institute, Academic Hospital Muenchen-Schwabing, Koelner Platz 1, D-80804, Munich Germany
SOURCE: Experimental and Clinical Endocrinology & Diabetes, (2000) Vol. 108, No. 3, pp. 181-189. print.
ISSN: 0947-7349.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A central finding of the UKPDS was that in type 2 diabetic patients, tight glycemic control with HbA1c targets as close to the normal range as possible must be achieved to further reduce diabetes related- **complications**, -mortality, and -**cardiovascular** disease, highlighting the need for new, optimized treatment strategies. With a focus on clinical efficacy, this paper discusses the results from the 20 major therapeutical trials published in the years 1997-1999, that evaluated the new insulinsensitizing thiazolidinediones Rosiglitazone and Pioglitazone and the new insulin-releasing potassium channel blockers Repaglinide and Nateglinide. While for Nateglinide, promising, but only preliminary data is available at current, Rosiglitazone, Pioglitazone, and Repaglinide have been shown appropriate for both mono- and combination therapy with current standard drug **treatment** of **type 2 diabetes**. Similar to the known, older antidiabetic drugs, the new agents discussed have comparable blood glucose lowering potentials with a dose-related capacity of 0.5 to 1.5% HbA1c reduction. These beneficial effects were both seen in drug-naive patients previously treated with diet only and in combination therapies where patients had previous antidiabetic standard drug treatment suggesting effectiveness of glitazones and glinides also in more advanced stages of the disease. Problems with adverse effects appeared minor although longe-range implications of weight gain, edema, lowering of hemoglobin, increase of total cholesterol for the glitazones, and hypoglycemia for glinides warrant further consideration. What becomes clear from the variety of most recent mono- and combination treatment studies with as much as five different classes of antidiabetic drugs is that individually tailored therapies that recognize quality of life parameters and target the predominant features of metabolic pathology (such as early postprandial

versus fasting hyperglycemia, degree of insulin resistance, progressive loss of beta-cell function) may become a feasible goal in the future.

L35 ANSWER 35 OF 41 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:85943 HCAPLUS
DOCUMENT NUMBER: 134:262751
TITLE: X-ceptors, nuclear receptors for metabolism
AUTHOR(S): Auwerx, Johan; Mangelsdorf, David
CORPORATE SOURCE: Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/ULP, Illkirch, F-67404, Fr.
SOURCE: International Congress Series (2001), 1215(Atherosclerosis XII), 21-39
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 118 refs. is given. The authors designate permissive RXR heterodimer partners as X-ceptors. These X-ceptors include nuclear receptors such as the peroxisome proliferator-activated **receptors** (PPAR), the **liver X receptors** (**LXR**), the pregnane **X receptor** or steroid and xenobiotic **receptor** (PXR/SXR), and the farnesol X receptor (FXR; also termed bile acid receptor or BAR). The ligands for these X-ceptors are found in excess (Xs) in humans in an industrialized westernized society and include compds. of dietary origin, such as fatty acids (PPARs) and sterols (LXRs), compds. induced by a western-style diet, such as bile acids (FXR), and drugs and xenobiotics (SXR, FXR). X-ceptors can therefore be considered as receptors for excess, or thrifty receptors, and they are thought to play an important role in many common disorders, such as obesity, insulin resistance, type 2 **diabetes**, hyperlipidemia, gallbladder disease, etc., often commonly referred to as "syndrome X". The central role of X-ceptors in common disorders makes them also excellent drug targets. The above points are illustrated by reviewing the biol. of PPAR.gamma., a master controller of adipogenesis, lipid and glucose homeostasis, and of **LXR** and FXR, which together control cholesterol and bile acid homeostasis.
REFERENCE COUNT: 118 THERE ARE 118 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 36 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:114572 BIOSIS
DOCUMENT NUMBER: PREV200000104572
TITLE: Reverse endocrinology as an approach to drug discovery.
AUTHOR(S): De Luca, Luigi M. (1)
CORPORATE SOURCE: (1) Differentiation Control Section, Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, 37 Convent Drive, Building 37, Room 5A/17, Bethesda, MD, 20892-4255 USA
SOURCE: Drugs of the Future, (Nov., 1999) Vol. 24, No. 11, pp. 1211-1219.
ISSN: 0377-8282.
DOCUMENT TYPE: Article
LANGUAGE: English

L35 ANSWER 37 OF 41 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999369734 EMBASE
TITLE: Novel **therapeutic** strategies for the **treatment** of **Type 2**

Kam 09/[illegible],744

diabetes.

AUTHOR: Perfetti R.; Barnett P.S.; Mathur R.; Egan J.M.
CORPORATE SOURCE: Dr. R. Perfetti, Division of Endocrinology Metabolism, Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 9[illegible]48, United States
SOURCE: Diabetes/Metabolism Reviews, [illegible], 14/3 (217-225).
Refs: 126
ISSN: 0742-4221 CODEN: DMREEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Diabetes mellitus is the most common endocrine disease, accounting for over [illegible] million people affected worldwide. It is characterized by a lack of insulin secretion and/or increased cellular resistance to insulin, resulting in hyperglycemia and other metabolic disturbances. People with diabetes suffer from increased morbidity and premature mortality related to **cardiovascular**, microvascular and neuropathic **complications**. The Diabetes Control and Complication Trial (DCCT) has convincingly demonstrated the relationship of hyperglycemia to the development and progression of complications and showed that improved glycemic control reduced these complications. Although the DCCT exclusively studied patients with Type 1 diabetes, there is ample evidence to support the belief that the same relationship between metabolic control and clinical outcome exists in patients with Type 2 diabetes. Therefore, a major effort should be made to develop and implement more effective treatment regimes. This article reviews those novel drugs that have been recently introduced for the management of Type 2 diabetes, or that have reached an advanced level of study and will soon be proposed for preliminary clinical trials. They include: (i) compounds that promote the synthesis/secretion of insulin by the .beta.-cell; (ii) inhibitors of the .alpha.-glucosidase activity of the small intestine; (iii) substances that enhance the action of insulin at the level of the target tissues; and (iv) inhibitors of free fatty acid oxidation.

L35 ANSWER 38 OF 41 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1998:182005 SCISEARCH
THE GENUINE ARTICLE: YZ065
TITLE: New patents and allowances
AUTHOR: ANON
SOURCE: BIOTECHNOLOGY LAW REPORT, (JAN-FEB 1998) Vol. 17, No. 1, pp. 20-26.
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538.
ISSN: 0278-4718.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L35 ANSWER 39 OF 41 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 97375343 MEDLINE
DOCUMENT NUMBER: 97375343 PubMed ID: 9216857
TITLE: Tissue distribution and quantification of the expression of mRNAs of peroxisome proliferator-activated **receptors** and **liver X receptor**-alpha in humans: no alteration in adipose

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tissue of obese and NIDDM patients.

AUTHOR: Auboeuf D; Rieusset J; Fajas L; Vallier P; Frering V; Riou J P; Staels B; Auwerx J; Laville M; Vidal H
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale (INSERM) U.449 and Lyon Human Nutrition Research Center, R. Laennec Faculty of Medicine, France.

SOURCE: DIABETES, 1997 Aug 46 (8) 1319-27.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970827
Last Updated on STN: 20021227
Entered Medline: 19970813

AB Members of the peroxisome proliferator-activated receptor (PPAR) family might be involved in pathologies with altered lipid metabolism. They participate in the control of the expression of genes involved in lipid metabolism and adipocyte differentiation. In addition, thiazolidinediones improve insulin resistance in vivo by activating PPAR gamma. However, little is known regarding their tissue distribution and relative expression in humans. Using a quantitative and sensitive reverse transcription (RT)-competitive polymerase chain reaction (PCR) assay, we determined the distribution and relative mRNA expression of the four PPARs (alpha,beta, gamma1, and gamma2) and **liver X receptor**-alpha (**LXR** alpha) in the main tissues implicated in lipid metabolism. PPAR alpha and **LXR** alpha were mainly expressed in liver, while PPAR gamma1 predominated in adipose tissue and large intestine. We found that PPAR gamma2 mRNA was a minor isoform, even in adipose tissue, thus causing question of its role in humans. PPAR beta mRNA was present in all the tissues tested at low levels. In addition, PPAR gamma mRNA was barely detectable in skeletal muscle, suggesting that improvement of insulin resistance with thiazolidinediones may not result from a direct effect of these agents on PPAR gamma in muscle. Obesity and NIDDM were not associated with change in PPARs and **LXR** alpha expression in adipose tissue. The mRNA levels of PPAR gamma1, the predominant form in adipocytes, did not correlate with BMI, leptin mRNA levels, or fasting insulinemia in 29 subjects with various degrees of obesity. These results indicated that obesity is not associated with alteration in PPAR gene expression in abdominal subcutaneous adipose tissue in humans.

L35 ANSWER 40 OF 41 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 97235676 MEDLINE
DOCUMENT NUMBER: 97235676 PubMed ID: 9121188
TITLE: Sensitization of **diabetic** and obese mice to insulin by retinoid X receptor agonists.
AUTHOR: Mukherjee R; Davies P J; Crombie D L; **Bischoff E D**; Cesario R M; Jow L; Hamann L G; Boehm M F; Mondon C E; Nadzan A M; Paterniti J R Jr; Heyman R A
CORPORATE SOURCE: Department of Cardiovascular Research, Ligand Pharmaceuticals, San Diego, California 92121, USA.
SOURCE: NATURE, 1997 Mar 27) 386 (6623) 407-10.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

Search completed by David Schreiber 308-4292

Ram 09/982,144

ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970506
Last Updated on STN: 20030318
Entered Medline: 19970418

AB Retinoic acid receptors (RAR), thyroid hormone receptors (TR), peroxisome proliferator activated receptors (PPARs) and the orphan receptor, **LXR**, bind preferentially to DNA as heterodimers with a common partner, retinoid X receptor (RXR), to regulate transcription. We investigated whether RXR-selective agonists replicate the activity of ligands for several of these receptors? We demonstrate here that RXR-selective ligands (referred to as rexinoids) function as RXR heterodimer-selective agonists, activating RXR: PPARgamma and RXR: **LXR** dimers but not RXR:RAR or RXR:TR heterodimers. Because PPARgamma is a target for antidiabetic agents, we investigated whether RXR ligands could alter insulin and glucose signalling. In mouse models of noninsulin-dependent **diabetes** mellitus (NIDDM) and obesity, RXR agonists function as insulin sensitizers and can decrease hyperglycaemia, hypertriglyceridaemia and hyperinsulinaemia. This antidiabetic activity can be further enhanced by combination treatment with PPARgamma agonists, such as thiazolidinediones. These data suggest that the RXR:PPARgamma heterodimer is a single-function complex serving as a molecular target for **treatment** of **insulin resistance**. Activation of the RXR:PPARgamma dimer with rexinoids may provide a new and effective treatment for NIDDM.

L35 ANSWER 41 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:[illegible] BIOSIS
DOCUMENT NUMBER: PREV199799[illegible]
TITLE: Novel pharmacological approaches to the prevention and **treatment** of non-insulin-dependent **diabetes** mellitus.
AUTHOR(S): Meier, Christoph A.
CORPORATE SOURCE: Div. Genetics, Thorn 905, Brigham Women's Hosp., 20 Shattuck Street, Boston, MA 02115 USA
SOURCE: European Journal of Endocrinology, (1997) Vol. 137, No. 3, pp. 224-225.
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